

Exhibit A



US005583122A

United States Patent [19]**Benedict et al.**[11] **Patent Number:** **5,583,122**[45] **Date of Patent:** **Dec. 10, 1996**[54] **PHARMACEUTICAL COMPOSITIONS
CONTAINING GEMINAL DIPHOSPHONATES**[75] **Inventors:** James J. Benedict, Norwich, N.Y.;
Christopher M. Perkins, Cincinnati,
Ohio[73] **Assignee:** The Procter & Gamble Company,
Cincinnati, Ohio

100718	2/1984	European Pat. Off.
0170228	2/1986	European Pat. Off.
2343476	4/1975	Germany
2513966	10/1976	Germany
2541981	3/1977	Germany
53-59674	5/1978	Japan
54-135724	10/1979	Japan
55-98193	7/1980	Japan
2004888	4/1979	United Kingdom

OTHER PUBLICATIONS[21] **Appl. No.:** 806,155[22] **Filed:** Dec. 6, 1985**Related U.S. Application Data**[63] **Continuation-in-part of Ser. No. 684,543, Dec. 21, 1984,
abandoned**[51] **Int. Cl.⁶** C07F 9/38; C07F 9/58;
A61K 31/675[52] **U.S. Cl.** 514/89; 546/22[58] **Field of Search** 514/89; 546/23,
546/22[56] **References Cited****U.S. PATENT DOCUMENTS**

3,553,314	1/1971	Francis	424/49
3,683,080	8/1972	Francis	514/107
3,846,420	11/1974	Wollmann et al.	544/157
3,941,772	3/1976	Ploger et al.	546/6
3,957,160	5/1976	Ploger et al.	210/58
3,960,888	6/1976	Ploger et al.	548/412
3,979,385	9/1976	Wollmann et al.	544/157
3,988,443	10/1976	Ploger et al.	514/79
4,034,086	7/1977	Ploger et al.	514/91
4,100,167	7/1978	Selvarajan et al.	260/296 R
4,117,090	9/1978	Ploger	423/268
4,134,969	1/1979	Schmidt-Dunker	424/49
4,239,695	12/1980	Chai et al.	260/502.5
4,267,108	5/1981	Blum et al.	260/326.61
4,304,734	12/1981	Jary et al.	562/13
4,407,761	10/1983	Blum et al.	562/13
4,447,255	5/1984	Suzuki et al.	71/86
4,447,256	5/1984	Suzuki et al.	71/86
4,473,560	9/1984	Biere et al.	514/95
4,503,049	3/1985	Biere et al.	514/80
4,608,368	8/1986	Blum et al.	514/107
4,621,077	11/1986	Rosini et al.	514/108
4,687,767	8/1987	Bosics et al.	514/89
4,687,768	8/1987	Benedict et al.	514/102
4,696,920	9/1987	Bentzen et al.	514/89
4,719,203	1/1988	Bosics et al.	514/108
4,777,163	10/1988	Bosics et al.	514/80

FOREIGN PATENT DOCUMENTS

88359 9/1983 European Pat. Off.

C.A. vol. 93(1980) 93: 232711f, Nissan Chem. Ind.

C.A. vol.93(1980) 93: 199,239h, Nissan Chem. Ind.

Worms Q.A. vol. 77 (1972) 130478N.

C.A. vol. 94(1981) 94:11638f Nissan Chem. Ind.

Francis & Martodam, "Chemical, Biochemical, & Medicinal Properties of the Diphosphonates", in *The Role of Phosphonates in Living Systems* (CRC Press; Hilderbrand editor), pp. 55-96 (1983).

Unterspann, "Experimental Examinations on the Suitability of Organoaminomethane-bis-Phosphonic Acids for Bone-Scintigraphy by Means of Tc-99m in Animals", Eur. J. Nucl. Med., vol. 1, pp. 151-154 (1976).

Sologub et al., "Synthesis and Intramolecular Electronic Interactions in Molecules of Tetrachloropyridyl-4-carbonimido-yl Dichloride and Its Derivatives", Khim. Geterotsikl. Soedin, 1983, (6), pp. 798-800; abstract attached Chem. Abs. 99:122,246z.

Maier, "Organophosphorous Compounds. Part 75", Phosphorus Sulfur, vol. 11 (3), pp. 311-22 (1981); abstract attached Chem. Abst. 96:52398n, plus article.

Ploeger et al., "Preparation of 1-Aminoalkylidene Diphosphonic Acids", Z. Anorg. Allg. Chem., vol. 389 (2), pp. 119-28 (1972); (original and English translation attached).

Grapov et al., "Reaction of Ethyl-N-2-pyridylimidoformate with Dialkylphosphites" Zh. Obshch. Khim., vol. 57 (7), pp. 1655-1657 (1980); abstract attached Chem. Abst. 93:220, 855t.

Bandurina et al., "Synthesis of Some Aminophosphonic Acids and Their Antineoplastic Activity", Khim.-Farm. Zh., vol. 12 (11), pp. 35-37 (1978); Chem. Abst. 90:115,081c.

Primary Examiner—Alan L. Rotman**Attorney, Agent, or Firm**—K. W. Zerby; David L. Suter[57] **ABSTRACT**

Pharmaceutical compositions, useful for treating abnormal calcium and phosphate metabolism, which contain geminal-diphosphonic acid compounds; and a method of treating diseases characterized by abnormal calcium and phosphate metabolism utilizing these pharmaceutical compositions.

23 Claims, No Drawings

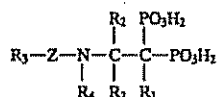
5,583,122

17

N-(2-(5-chloro)-pyridyl)-aminomethane diphosphonic acid;
 N-(2-(3-picolyl))-aminomethane diphosphonic acid;
 N-(2-(4-picolyl))-aminomethane diphosphonic acid;
 N-(2-(5-picolyl))-aminomethane diphosphonic acid;
 N-(2-(6-picolyl))-aminomethane diphosphonic acid;
 N-(2-(3,4-lutidine))-aminomethane diphosphonic acid;
 N-(2-pyrimidyl)-aminomethane diphosphonic acid;
 N-(2-pyridyl)-2-aminoethane-1,1-diphosphonic acid;
 2-(3-pyridyl)-ethane-1,1-diphosphonic acid;
 2-(4-pyridyl)-ethane-1,1-diphosphonic acid;
 2-(2-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid;
 2-(3-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid;
 2-(4-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid;
 O-(2-(3-picolyl))-oxamethane-diphosphonic acid; or pharmaceutically-acceptable salts or esters thereof.

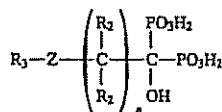
What is claimed is:

1. A diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, having the structure:



wherein Z is a pyridine ring; R₁ is hydrogen substituted or unsubstituted amino, amido, hydroxy, C₁-C₆ alkoxy, halogen, carboxylate, a substituted or unsubstituted, a saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R₂ is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; R₃ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C₁-C₆ alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and R₄ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms, or acetyl; and wherein said substituted R₁, R₂, R₃ and R₄ groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate.

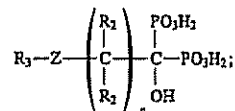
2. A diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, having the structure:



wherein Z is a pyridine ring; n is 0 or 1; R₂ is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; and R₃ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C₁-C₆ alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and wherein said substituted R₂ and R₃ groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate.

18

3. A diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, having the structure:

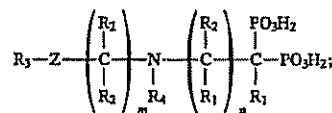


wherein Z is a pyridine ring n is 1; R₂ is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; and R₃ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C₁-C₆ alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and wherein said substituted R₂ and R₃ groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate.

4. A diphosphonic acid compound, or pharmaceutically-acceptable salt or ester thereof, which is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid.

5. A pharmaceutical composition comprising:

(a) a geminal diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 mg of phosphorus in said composition, wherein said diphosphonic acid compound is of the formula:



wherein Z is a pyridine ring; m+n is an integer from 0 to 5; R₁ is hydrogen, substituted or unsubstituted amino, amido, hydroxy, C₁-C₆ alkoxy, halogen, carboxylate, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl, except that when n=0, then R₁ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R₂ is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; R₃ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C₁-C₆ alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and R₄ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms, or acetyl;

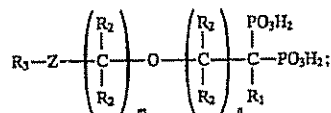
(b) a pharmaceutically-acceptable carrier.

6. A pharmaceutical composition comprising:

(a) a geminal diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 mg of phosphorus in said composition, wherein said diphosphonic acid compound is of the formula:

5,583,122

19



5

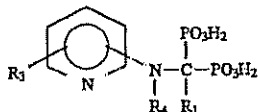
wherein Z is a pyridine ring; m+n is an integer from 0 to 5; R₁ is hydrogen, substituted or unsubstituted amino, amido, hydroxy, C₁-C₆ alkoxy, halogen, carboxylate, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl, except that when n=0, then R₁ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R₂ is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; and R₃ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C₁-C₆ alkoxy, amino, substituted amino, substituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and

(b) a pharmaceutically-acceptable carrier.

7. A pharmaceutical composition according to claim 5, wherein m+n=0.

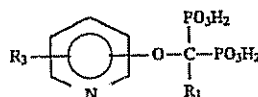
8. A pharmaceutical composition according to claim 6, wherein m+n=0.

9. A pharmaceutical composition according to claim 7, wherein said diphosphonic acid compound is of the formula:



wherein R₁ is hydrogen; R₃ is hydrogen, methyl, amino, chloro, methoxy, nitro, or hydroxy; and R₄ is hydrogen, methyl, or ethyl.

10. A pharmaceutical composition according to claim 8, wherein said diphosphonic acid compound is of the formula:

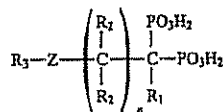


wherein R₁ is hydrogen, and R₃ is hydrogen, methyl, amino, chloro, methoxy, nitro, or hydroxy.

11. A pharmaceutical composition comprising:

(a) a geminal diphosphonic acid compound or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 milligrams phosphorus in said composition, wherein said compound is of the formula:

20

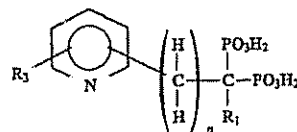


wherein Z is a pyridine ring; n is 0 or 1; R₁ is hydrogen, substituted or unsubstituted amino, amido, hydroxy, C₁-C₆ alkoxy, halogen, carboxylate, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R₂ is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; and R₃ is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C₁-C₆ alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and wherein said substituted R₁, R₂ and R₃ groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate; and

(b) a pharmaceutically-acceptable carrier.

12. A pharmaceutical composition according to claim 11, wherein n=1.

13. A pharmaceutical composition according to claim 11, wherein said diphosphonic acid compound is of the formula:



wherein n=0 or 1; R₁ is hydrogen, chloro, amino, or hydroxy; and R₃ is hydrogen, methyl, amino, chloro, methoxy, hydroxy, or nitro.

14. A pharmaceutical composition according to claim 12, wherein said diphosphonic acid compound is selected from the group consisting of 2-(2-pyridyl)-ethane-1,1-diphosphonic acid; 2-(3-pyridyl)-ethane-1,1-diphosphonic acid; 2-(4-pyridyl)-ethane-1,1-diphosphonic acid; 2-(2-pyridyl)-hydroxyethane-1,1-diphosphonic acid; 2-(3-pyridyl)-hydroxyethane-1,1-diphosphonic acid; and 2-(4-pyridyl)-hydroxyethane-1,1-diphosphonic acid.

15. A pharmaceutical composition according to claim 14, wherein said diphosphonic acid compound is 2-(2-pyridyl)-ethane-1,1-diphosphonic acid.

16. A pharmaceutical composition according to claim 14, wherein said diphosphonic acid compound is 2-(3-pyridyl)-hydroxyethane diphosphonic acid.

17. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 5.

18. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 6.

19. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising admin-

5,583,122

21

istering to a person in need of such treatment a safe and effective amount of a composition of claim 7.

20. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 12. 5

21. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 14.

22

22. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 15.

23. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 16.

* * * * *

Exhibit B



US005994329A

United States Patent [19]

Daifotis et al.

[11] Patent Number: 5,994,329

[45] Date of Patent: Nov. 30, 1999

[54] **METHOD FOR INHIBITING BONE RESORPTION**

[75] Inventors: Anastasia G. Daifotis, Westfield; Arthur C. Santora, II, Watchung; A. John Yates, Westfield, all of N.J.

[73] Assignee: Merck & Co., Inc., Rahway, N.J.

[21] Appl. No.: 09/134,214

[22] Filed: Aug. 14, 1998

Related U.S. Application Data

[63] Continuation of application No. PCT/US98/14796, Jul. 17, 1998.

[60] Provisional application No. 60/053,535, Jul. 23, 1997, and provisional application No. 60/053,351, Jul. 22, 1997.

[51] Int. Cl.⁶ A61K 31/66

[52] U.S. Cl. 514/108

[58] Field of Search 514/108

[56] **References Cited****U.S. PATENT DOCUMENTS**

4,425,339	1/1984	Pitchford	424/239
4,621,077	11/1986	Rosini et al.	514/108
4,761,406	8/1988	Flora et al.	514/86
4,812,304	3/1989	Anderson et al.	424/112
4,822,609	4/1989	Flora	424/112
4,980,171	12/1990	Fels et al.	424/473
5,270,365	12/1993	Gertz et al.	514/108
5,366,965	11/1994	Strein	514/102
5,488,041	1/1996	Burbier et al.	514/108
5,616,560	4/1997	Geddes et al.	514/12
5,773,429	6/1998	Fuiz	514/102
5,780,455	7/1998	Brenner et al.	514/108

FOREIGN PATENT DOCUMENTS

0 274 158	7/1988	European Pat. Off.
0 600 834 A1	6/1994	European Pat. Off.
WO 94/00129	1/1994	WIPO
WO 94/00130	1/1994	WIPO
WO 94/21242	9/1994	WIPO
WO 95/08331	3/1995	WIPO
WO 95/28145	10/1995	WIPO
WO 95/28936	11/1995	WIPO
WO 95/30421	11/1995	WIPO
WO 96/17616	6/1996	WIPO

OTHER PUBLICATIONSSinger et al., *Advances in Endocrin. & Metab.*, vol. 6 (1995), pp. 259-288, "Bisphosphonates in the treatment of disorders of mineral metabolism".Lieberman et al., *N. Eng. J. of Medicine*, vol. 333 (1995), pp. 1437-1443, "Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis".Bankhurst et al., *Arthritis and Rheumatism*, vol. 38, No. 9, Suppl. 1 (1995), S359, "Three-year treatment with alendronate prevents fractures in women with postmenopausal osteoporosis".Filippini et al., *J. of Bone & Min. Research*, vol. 10 (1995), pp. 697-703, "Cyclical clodronate is effective in preventing postmenopausal bone loss: A comparative study with transcutaneous hormone replacement therapy".McClung et al., *Bone*, vol. 17 (1995), pp. 493S-496S, "Tiludronate therapy for Paget's disease of bone".Seltenmeyer et al., *Bone (NY)*, vol. 20, No. 4, Suppl., (1997) pp. 114S, "A comparison of the antiresorptive potency of various bisphosphonates in vivo with their inhibitory effect in vitro on squalene synthase and cellular sterol synthesis". Adachi et al., *Today's Therapeutic Trends*, vol. 14, No. 1 (1996), pp. 13-24, "Osteoporosis—Its diagnosis, management and treatment with a new oral bisphosphonate agent, etidronate".Bell et al., *Endocrine*, vol. 6(2) (1997), pp. 203-206, "Bisphosphonates in the Treatment of Osteoporosis".

Lunar News, Apr. 1997, "Update: Bisphosphonate", pp. 30-32.

Gertz et al., *Osteoporosis Int.* (1993), Suppl. 3: S13-16, "Clinical pharmacology of alendronate sodium".Gertz et al., *Clin. Pharma. Ther.* (1995), vol. 58, pp. 288-298, "Studies of the oral bioavailability of alendronate".de Vernejoul et al., *Calcified Tissue Int'l*, vol. 40 (1987), pp. 160-165, "Different schedules of administration of (3 amino-1-hydroxypropylidene)-1,1-bisphosphonate induce different changes".Lufkin et al., *Osteoporosis Int'l*, (1994), vol. 4, pp. 320-322, "Pamidronate: An unrecognized problem in gastrointestinal tolerability".De Groen et al., *N. England J. of Medicine*, (1996), vol. 335, pp. 1016-1021, "Esophagitis associated with the use of alendronate".Castell, (an editorial), *N. England J. of Medicine* (1996), vol. 335, pp. 1058-1059, "Pill esophagitis—the case of alendronate".Lieberman et al., (correspondence), *N. England J. of Medicine* (1996), vol. 335, pp. 1069-1070, "Esophagitis and alendronate".Chesnut et al., *Am. J. of Medicine*, vol. 99 (1995), pp. 144-152, "Alendronate treatment of the postmenopausal osteoporotic woman".Cassidy et al., *Digestive Diseases and Sciences*, vol. 37 (1992), pp. 1206-1211, "Continuous versus intermittent acid exposure in production of esophagitis in feline model".Mortensen et al., *J. of Bone & Mineral Res.*, (1995) vol. 10, suppl. 1, p. s140, "Prevention of early postmenopausal bone loss by risedronate".Harris et al., *J. of Clin. Endoc. & Metab.*, 76:1399-1406 (1993), "The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone".Melsen et al., *Osteoporosis*, Chapt. 60 (1996), pp. 1145-1158, "ADFR—The Concept and its performance".

(List continued on next page)

Primary Examiner—Theodore J. Criares*Attorney, Agent, or Firm*—Anthony D. Sabatelli; Melvin Winokur

[57]

ABSTRACT

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

44 Claims, 8 Drawing Sheets

5,994,329

19

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

Example 7

Bisphosphonate tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Pat. No. 5,358,941, to Bechard et al., issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68mg	182.72g
Anhydrous Lactose, NF	71.32mg	285.28g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

Example 8

Liquid Bisphosphonate Formulation.

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

Ingredient	Weight
Alendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1N Sodium Hydroxide (eq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g.

20

about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A method for inhibiting bone resorption in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

2. A method according to claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

3. A method according to claim 2 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

4. A method according to claim 3 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

5. A method according to claim 2 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

6. A method according to claim 4 wherein said mammal is a human.

7. A method according to claim 6 wherein said dosing interval is once-weekly.

8. A method according to claim 7 wherein said unit dosage of said bisphosphonate comprises from about 17.5 mg to about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

9. A method according to claim 8 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

10. A method according to claim 6 wherein said dosing interval is twice-weekly.

11. A method according to claim 10 wherein said unit dosage of said bisphosphonate comprises from about 8.75 mg to about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

12. A method according to claim 6 wherein said dosing interval is biweekly.

13. A method according to claim 12 wherein said unit dosage of said bisphosphonate comprises from about 35 mg to about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

14. A method according to claim 6 wherein said dosing interval is twice-monthly.

15. A method according to claim 14 wherein said unit dosage of said bisphosphonate comprises about 35 mg to about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

16. A method for treating osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting

5,994,329

21

of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

17. A method according to claim 16 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

18. A method according to claim 17 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

19. A method according to claim 18 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

20. A method according to claim 17 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

21. A method according to claim 19 wherein said mammal is a human.

22. A method according to claim 21 wherein said dosing interval is once-weekly.

23. A method according to claim 22 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

24. A method according to claim 21 wherein said dosing interval is twice-weekly.

25. A method according to claim 24 wherein said unit dosage of said bisphosphonate comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

26. A method according to claim 21 wherein said dosing interval is biweekly.

27. A method according to claim 26, wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

28. A method according to claim 21 wherein said dosing interval is twice-monthly.

29. A method according to claim 28 wherein said unit dosage of said bisphosphonate comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

30. A method for preventing osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting

22

of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

31. A method according to claim 30 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

32. A method according to claim 31 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

33. A method according to claim 32 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

34. A method according to claim 31 wherein said bisphosphonate is selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

35. A method according to claim 33 wherein said mammal is a human.

36. A method according to claim 35 wherein said dosing interval is once-weekly.

37. A method according to claim 36 wherein said bisphosphonate unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

38. A method according to claim 35 wherein said dosing interval is twice-weekly.

39. A method according to claim 38 wherein said bisphosphonate unit dosage comprises about 17.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

40. A method according to claim 35 wherein said dosing interval is biweekly.

41. A method according to claim 40 wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

42. A method according to claim 35 wherein said dosing interval is twice-monthly.

43. A method according to claim 42 wherein said bisphosphonate unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

44. A kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

* * * * *

Exhibit C



US006432932B1

(12) **United States Patent**
Daifotis et al.

(10) Patent No.: **US 6,432,932 B1**
(45) Date of Patent: ***Aug. 13, 2002**

(54) **METHOD FOR INHIBITING BONE RESORPTION**

(75) Inventors: Anastasia G. Daifotis, Westfield;
Arthur C. Santora, II, Watchung; A.
John Yates, Westfield, all of NJ (US)

(73) Assignee: Merck & Co., Inc., Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 09/388,659

(22) Filed: Sep. 2, 1999

Related U.S. Application Data

(63) Continuation-in-part of application No. PCI/US98/14796, filed on Jul. 17, 1998.

(60) Provisional application No. 60/053,535, filed on Jul. 23, 1997, now abandoned, and provisional application No. 60/053,351, filed on Jul. 22, 1997, now abandoned.

(51) Int. Cl.⁷ A61K 31/66

(52) U.S. Cl. 514/108

(58) Field of Search 514/108

(56) References Cited

U.S. PATENT DOCUMENTS

4,425,339 A	1/1984	Pitchford	424/239
4,621,077 A	11/1986	Rosini et al.	514/108
4,761,406 A	8/1988	Flora et al.	514/86
4,812,304 A	3/1989	Anderson et al.	424/112
4,812,311 A	3/1989	Uchtman	
4,822,609 A	4/1989	Flora	424/112
4,927,814 A	5/1990	Gall et al.	
4,980,171 A	12/1990	Fels et al.	424/473
5,227,506 A	7/1993	Saari et al.	
5,270,365 A	12/1993	Gertz et al.	514/108
5,358,941 A	10/1994	Bechard et al.	
5,366,965 A	11/1994	Strein	514/102
5,488,041 A	1/1996	Barbier et al.	514/108
5,583,122 A	12/1996	Benedict et al.	
5,616,560 A	4/1997	Geddes et al.	514/12
5,616,571 A	4/1997	Daifotis et al.	
5,622,721 A	4/1997	Dansereau et al.	
5,773,429 A	6/1998	Fuisz	514/102
5,780,455 A	7/1998	Brenner et al.	514/108
5,804,570 A	9/1998	Santora, II et al.	
5,853,759 A	12/1998	Kaldare et al.	
5,994,329 A	* 11/1999	Daifotis et al.	514/108

FOREIGN PATENT DOCUMENTS

EP	0 274 158	7/1988
EP	0 600 834 A1	6/1994
WO	WO 93/11786	6/1993
WO	WO 94/00129	1/1994
WO	WO 94/00130	1/1994
WO	WO 94/21242	9/1994
WO	WO 95/08331	3/1995
WO	WO 95/28145	10/1995
WO	WO 95/28936	11/1995

WO	WO 95/30421	11/1995
WO	WO 96/17616	6/1996
WO	WO 96/25166	8/1996

OTHER PUBLICATIONS

Khan et al., Bone, vol. 20 (1997), pp. 263-271, "Alendronate in the treatment of Paget's disease of bone".

Physician's Desk Reference, 51st ed. (1997), pp. 1703-1706, "Fosamax".

Gertz et al., J. of Bone & Min. Res., vol. 9 (1994), pp. 135-142, "Monitoring bone resorption in early postmenopausal women by an immunoassay for cross-linked collagen peptides in urine".

Fleisch, J. of Clin. Endoc. & Metab., vol. 76 (1993), pp. 1397-1398, "Editorial: Prospective use of bisphosphonates in osteoporosis".

Chestnut et al., Osteoporosis Int'l (1993), Suppl. 3: S17-19, "Short-term effect of alendronate on bone mass and bone remodeling in postmenopausal women".

Gertz et al., J. of Bone & Min. Res., vol. 6, Suppl. 1 (1991), Abstract No. 790, p. S281, "Oral bioavailability and dose proportionality of alendronate (aminohydroxybutylidene bisphosphonate) in postmenopausal women".

Mortensen et al., J. Bone & Min. Res., (1995) 10 (Supp. 1): S360, "Prevention of early postmenopausal bone loss by risedronate: A two year study".

Actonel™ (risedronate sodium tablets) package insert, dated Mar. 1998.

Lunar News, Apr. 1997, "Update: Bisphosphonate", pp. 30-32.

Gertz et al., Osteoporosis Int. (1993), Suppl. 3: S13-16, "Clinical pharmacology of alendronate sodium".

Gertz et al., Clin. Pharma. Ther. (1995), vol. 58, pp. 288-298, "Studies of the oral bioavailability of alendronate".

Singer et al., Advances in Endocrin. & Metab., vol. 6 (1995), pp. 259-288, "Bisphosphonates in the treatment of disorders of mineral metabolism".

Lieberman et al., N. Eng. J. of Medicine, vol. 333 (1995), pp. 1437-1443, Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal.

Bankhurst et al., Arthritis and Rheumatism, vol. 38, No. 9, Suppl. 1 (1995), S359, Three-year treatment with alendronate prevents fractures in women with postmenopausal.

de Vernejoul et al., Calcified Tissue Int'l, vol. 40 (1987), pp. 160-165, "Different schedules of administration of (3 amino-1-hydroxypropylidene)-1,1-bisphosphonate induce different changes . . .".

(List continued on next page)

Primary Examiner—Theodore J. Criares

(74) Attorney, Agent, or Firm—J. Antonio Garcia-Rivas; Mark R. Daniel

(57)

ABSTRACT

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

20 Claims, 8 Drawing Sheets

US 6,432,932 B1

19

patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably about once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 5

Twice-monthly Dosing Regimen
Treatment of Osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of Osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Example 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

Example 7

Bisphosphonate Tablets

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in

20

U.S. Pat. No. 5,358,941, to Bechard et al, issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
Anhydrous Lactose, NF	71.32 mg	285.28 g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

Example 8

Liquid Bisphosphonate Formulation.

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

Ingredient	Weight
Alendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1 N Sodium Hydroxide (aq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A method for treating or preventing osteoporosis in a mammal, said method comprising orally administering to

US 6,432,932 B1

21

said mammal a pharmaceutically effective amount of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

2. A method according to claim 1 wherein said mammal is a human.

3. A method according to claim 2 wherein said dosing interval is once-weekly.

4. A method according to claim 3 wherein said unit dosage comprises from about 3.5 mg to about 200 mg, on an acid active basis, of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

5. A method according to claim 4 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

6. A method according to claim 4 wherein said unit dosage comprises about 35 mg, on an acid active basis, of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

7. A method according to claim 4 wherein said unit dosage comprises about 40 mg, on an acid active basis, of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

8. A method according to claim 4 wherein said unit dosage comprises about 45 mg, on an acid active basis, of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

9. A method according to claim 4 wherein said unit dosage comprises about 50 mg, on an acid active basis, of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

22

10. A method according to claim 6 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

11. A method according to claim 7 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

12. A method according to claim 8 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

13. A method according to claim 9 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

14. A method according to claim 3 wherein said unit dosage comprises about 1.5 to about 6000 $\mu\text{g/kg}$ body weight of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

15. A method according to claim 3 wherein said unit dosage comprises about 10 to about 2000 $\mu\text{g/kg}$ body weight of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

16. A method according to claim 14 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

17. A method according to claim 15 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate.

18. A method according to any one of claims 1-17 wherein said unit dosage is in the form of a tablet.

19. A method according to any one of claims 1-17 wherein said unit dosage is in the form of a capsule.

20. A method according to any one of claims 1-17 wherein said unit dosage is in the form of a liquid.

* * * * *

Exhibit D



US006465443B2

(12) **United States Patent**
Daifotis et al.

(10) Patent No.: **US 6,465,443 B2**
(45) Date of Patent: **Oct. 15, 2002**

(54) **METHOD FOR INHIBITING BONE RESORPTION**

(75) Inventors: **Anastasia G. Daifotis, Westfield, NJ (US); Arthur C. Santora, II, Watchung, NJ (US); A. John Yates, Westfield, NJ (US)**

(73) Assignee: **Merck & Co., Inc., Rahway, NJ (US)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 28 days.

(21) Appl No.: **09/812,450**

(22) Filed: **Mar. 20, 2001**

(65) **Prior Publication Data**

US 2001/0018431 A1 Aug. 30, 2001

Related U.S. Application Data

(60) Division of application No. 09/388,659, filed on Sep. 2, 1999, which is a continuation-in-part of application No. PCT/US98/14796, filed on Jul. 17, 1998

(60) Provisional application No. 60/053,535, filed on Jul. 23, 1997, and provisional application No. 60/053,351, filed on Jul. 22, 1997.

(51) Int. Cl.⁷ **A61K 31/66**

(52) U.S. Cl. **514/108**

(58) Field of Search **514/108**

(56) References Cited

U.S. PATENT DOCUMENTS

4,425,339 A 1/1984 Pitchford
4,621,077 A 11/1986 Rosini et al.
4,761,406 A 8/1988 Flora et al.
4,812,304 A 3/1989 Anderson et al.
4,812,311 A 3/1989 Uchtmann
4,822,609 A 4/1989 Flora
4,927,814 A 5/1990 Gall et al.
4,980,171 A 12/1990 Fels et al.
5,227,506 A 7/1993 Saari et al.
5,270,365 A 12/1993 Gertz et al.
5,358,941 A 10/1994 Bechard et al.
5,366,965 A 11/1994 Strein
5,488,041 A 1/1996 Barbier et al.
5,583,122 A 12/1996 Benedict et al.
5,616,560 A 4/1997 Geddes et al.
5,616,571 A 4/1997 Daifotis et al.
5,622,721 A 4/1997 Dansereau et al.
5,773,429 A 6/1998 Fuiz
5,780,455 A 7/1998 Brenner et al.
5,804,570 A 9/1998 Santora, II et al.
5,853,759 A 12/1998 Kaldare et al.
5,994,329 A 11/1999 Daifotis et al.

FOREIGN PATENT DOCUMENTS

EP 0 274 158 7/1988
EP 0 600 834 A1 6/1994
WO WO 93/11786 6/1993
WO WO 94/00129 1/1994
WO WO 94/00130 1/1994
WO WO 94/21242 9/1994
WO WO 95/08331 3/1995

WO WO 95/28145 10/1995
WO WO 95/28936 11/1995
WO WO 95/30421 11/1995
WO WO 96/17616 6/1996
WO WO 96/25166 8/1996

OTHER PUBLICATIONS

Lunar News (Jul. 1996), "Update: Bisphosphonate", pp. 23-24.

Lunar News (Apr. 1996), "Update: Bisphosphonate", p. 31.
The Pink Sheet (Dec. 18, 1995), vol. 57, Issue 51, "Merck Cozaar generating 25,000 scripts weekly after six months on market; Fosamax off to quick start, company tells securities analyst meeting".

Scrip (Nov. 24, 1999), "Merck develops once-weekly Fosamax".

Baran, Geriatrics, vol. 56, No. 3 (Mar. 2001), pp. 28-32, "Osteoporosis: Efficacy and safety of a bisphosphonate dosed once weekly".

Bone et al., Clinical Therapeutics, vol. 22, No. 1 (2000), pp. 15-28, "Weekly administration of alendronate: Rationale and plan for clinical assessment".

Fleisch, Expert Opinion Therapeutic Patents, vol. 11, No. 9 (2000), pp. 1371-1381, "Bisphosphonates: mechanisms of action".

Peter et al., Journal of Pharmacology & Experimental Therapeutics, vol. 276, No. 1 (1996), p. 271-276, "Long-term safety of the aminobisphosphonate alendronate in adult dogs".

Rodan et al., Osteoporosis International (1993) Suppl. 3:S7-12, "Preclinical pharmacology of alendronate".

Schnitzer, Expert Opinion Pharmacother., vol. 2, No. 9 (2001), pp. 1461-1472, "Update on alendronate for osteoporosis: once-weekly dosing".

Schnitzer et al., Aging: Clinical and Experimental Research, vol. 12, No. 1 (2000), p. 1-12, "Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis".

Seedor et al., Journal of Bone & Mineral Research, vol. 6, No. 4 (1991), pp. 339-346, "The bisphosphonate alendronate (MK-217) inhibits bone loss due to ovariectomy in rats".

Sorrentino, Endoscopy, vol. 28 (1996), p. 529, "Esophageal ulceration due to alendronate".

Bone et al., Journal of Bone & Mineral Research, vol. 16, Suppl. 1 (Sep. 2001), M392, "Once-weekly alendronate: Two year subgroup efficacy analyses in postmenopausal women with osteoporosis".

(List continued on next page.)

Primary Examiner—Theodore J. Criarcs

(74) Attorney, Agent, or Firm—J. Antonio Garcia-Rivas; Mark R. Daniel

(57) ABSTRACT

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

54 Claims, 8 Drawing Sheets

US 6,465,443 B2

19

EXAMPLE 5

Twice-monthly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

EXAMPLE 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

EXAMPLE 7

Bisphosphonate tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Pat. No. 5,358,941, to Bechard et al., issued Oct. 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

Ingredient	Per Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
Anhydrous Lactose, NF	71.32 mg	285.28 g
Microcrystalline Cellulose, NF	80.0 mg	320.0 g
Magnesium Stearate, NF	1.0 mg	4.0 g
Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also,

20

tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

EXAMPLE 8

Liquid Bisphosphonate Formulation

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients

Ingredient	Weight
Alendronate Monosodium Trihydrate	91.35 mg
Sodium Propylparaben	22.5 mg
Sodium Butylparaben	7.5 mg
Sodium Citrate Dihydrate	1500 mg
Citric Acid Anhydrous	56.25 mg
Sodium Saccharin	7.5 mg
Water	qs 75 mL
1 N Sodium Hydroxide (eq)	qs pH 6.75

The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

What is claimed is:

1. A pharmaceutical composition comprising about 35 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
2. A pharmaceutical composition comprising about 40 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
3. A pharmaceutical composition comprising about 45 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
4. A pharmaceutical composition comprising about 50 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
5. A pharmaceutical composition comprising about 35 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
6. A pharmaceutical composition comprising about 40 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

US 6,465,443 B2

21

7. A pharmaceutical composition comprising about 45 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

8. A pharmaceutical composition comprising about 50 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

9. A pharmaceutical composition according to any one of claims 5-8 wherein said pharmaceutically acceptable salt is risedronate monosodium hemi-pentahydrate.

10. A kit comprising at least one pharmaceutically effective unit dosage of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, for oral administration to a mammal in need thereof according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

11. A kit according to claim 10 wherein said mammal is a human.

12. A kit according to claim 11 wherein said unit dosage comprises from about 1.5 to about 6000 μ g/kg body weight.

13. A kit according to claim 11 wherein said unit dosage comprises from about 10 to about 2000 μ g/kg body weight.

14. A kit according to claim 13 wherein said dosing interval is once-weekly.

15. A kit according to claim 14 wherein said unit dosage is in the form of a tablet.

16. A kit according to claim 15 wherein said kit is a blister pack.

17. A kit according to claim 16 which further comprises a memory aid for administering said unit dosages.

18. A kit according to claim 17 wherein said memory aid indicates that said unit dosages are administered once a week.

19. A kit according to claim 18 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use.

20. A kit according to claim 19 which further comprises a calcium supplement.

21. A kit according to claim 14 wherein said unit dosage is in the form of a capsule.

22. A kit according to claim 21 wherein said kit is a blister pack.

23. A kit according to claim 22 which further comprises a memory aid for administering said unit dosages.

24. A kit according to claim 23 wherein said memory aid indicates that said unit dosages are administered once a week.

25. A kit according to claim 24 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use.

26. A kit according to claim 25 which further comprises a calcium supplement.

27. A kit according to claim 14 wherein said unit dosage is in the form of a liquid.

28. A kit according to claim 27 which further comprises a memory aid for administering said unit dosages.

29. A kit according to claim 28 wherein said memory aid indicates that said unit dosages are administered once a week.

30. A kit according to claim 29 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use.

31. A kit according to claim 30 which further comprises a calcium supplement.

22

32. A kit comprising from about 7 mg to about 100 mg of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, on an acid active basis, for oral administration to a human in need thereof, according to a continuous schedule having a once-weekly dosing interval.

33. A kit according to claim 32 wherein said unit dosage comprises about 35 mg of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, on an acid active basis.

34. A kit according to claim 32 wherein said unit dosage comprises about 40 mg of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, on an acid active basis.

35. A kit according to claim 32 wherein said unit dosage comprises about 45 mg of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, on an acid active basis.

36. A kit according to claim 32 wherein said unit dosage comprises about 50 mg of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof, on an acid active basis.

37. A kit according to claim 33 wherein said unit dosage is in the form of a tablet.

38. A kit according to claim 37 wherein said kit is a blister pack.

39. A kit according to claim 38 which further comprises a memory aid for administering said unit dosages.

40. A kit according to claim 36 wherein said memory aid indicates that said unit dosages are administered once a week.

41. A kit according to claim 40 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use.

42. A kit according to claim 41 which further comprises a calcium supplement.

43. A kit according to claim 33 wherein said unit dosage is in the form of a capsule.

44. A kit according to claim 43 wherein said kit is a blister pack.

45. A kit according to claim 44 which further comprises a memory aid for administering said unit dosages.

46. A kit according to claim 45 wherein said memory aid indicates that said unit dosages are administered once a week.

47. A kit according to claim 46 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use.

48. A kit according to claim 47 which further comprises a calcium supplement.

49. A kit according to claim 33 wherein said unit dosage is in the form of a liquid.

50. A kit according to claim 49 which further comprises a memory aid for administering said unit dosages.

51. A kit according to claim 50 wherein said memory aid indicates that said unit dosages are administered once a week.

52. A kit according to claim 50 wherein said unit dosages are oriented in said pharmaceutical kit in the order of their intended use.

53. A kit according to claim 52 which further comprises a calcium supplement.

54. A kit according to any one of claims 10-53 wherein said pharmaceutically acceptable salt is risedronate monosodium hemi-pentahydrate.

* * * * *

Exhibit E

Westlaw

Not Reported in F.Supp.2d
 2004 WL 2002208 (D.Del.)
 (Cite as: 2004 WL 2002208 (D.Del.))

Page 1

Motions, Pleadings and Filings

Only the Westlaw citation is currently available

United States District Court,
 D. Delaware
 SYNGENTA SEEDS, INC , Plaintiff,
 v.
 MONSANTO COMPANY, DeKalb Genetics
 Corp , Pioneer Hi-Bred International, Inc ,
 Dow Agrosciences, L.L.C, and Mycogen Plant
 Science, Inc and Agrigenetics, Inc ,
 collectively d b a Mycogen Seeds, Defendants
No. C.A. 02-1331-SLR.

Aug 27, 2004
 Paul M Lukoff, Prickett, Jones & Elliott,
 Wilmington, DE, for Plaintiff

Richard L. Horwitz, Potter, Anderson & Corroon,
 LLP, for Defendants

MEMORANDUM ORDER

ROBINSON, J

I INTRODUCTION

*1 On July 25, 2002, plaintiff Syngenta Seeds, Inc , filed a complaint alleging defendants infringed three of its patents ("BTC I"). (D I 1) Discovery in the BTC I action concluded on July 14, 2004, and the case is scheduled for a jury trial on November 29, 2004 (D I 228)

As a result of past motions, this court has excluded allegations regarding plaintiff's product MON863 and refused to allow discovery of pending patent applications. (D I 213, 81)

On April 13, 2004, plaintiff filed another complaint against defendants ("BTC II") for infringement of United States Patent No. 6,720,488 (" '488 patent"), which is not at issue in the BTC I litigation Before

the court is plaintiff's motion to consolidate BTC II with the BTC I litigation (D I 205)

II BACKGROUND

On December 9, 2003, the United States Patent and Trademark Office ("PTO") issued a Notice of Allowance, which allowed the '488 patent to issue as soon as the issue fee was paid On April 13, 2004, the PTO issued the '488 patent. The next day plaintiff filed its BTC II complaint against defendants alleging infringement of the '488 patent. The action was filed with this court, Civ. No. 04-228, and marked as related to the BTC I litigation.

Prior to filing this motion to consolidate, plaintiff complied with Local Rul 7 1 1 and requested that defendants consent to the consolidation Defendants refused and this pending motion resulted

Plaintiff alleges that, after the issuance of the Notice of Allowance, it notified defendants Monsanto and DeKalb that an additional patent application was pending and provided them with a copy of the allowed patent claims and notice Defendants contest this assertion and note that the claims of the '488 patent were not included in discovery or depositions, including those taken after the PTO issued the allowance notice (D I 215 at 5)

The '488 patent has the following in common with the patents at issue in BTC I:

- (1) '488 was the result of a continuation patent application of '100 patent;
- (2) It relates to the expression of *Bt* genes in corn;
- (3) The specifications for the '100 and '488 patents are "virtually identical" (D I 206);
- (4) Both the '100 and '488 inventions were created by the same inventors; and
- (5) The '488 patent is terminally disclaimed over the '100 and '185 patents.

III DISCUSSION

Federal Rule of Civil Procedure 42(a) provides this

Not Reported in F.Supp.2d
 2004 WL 2002208 (D Del.)
 (Cite as: 2004 WL 2002208 (D.Del.))

Page 2

court with authority to consolidate "actions involving a common question of law or fact pending before the court." Whether or not to consolidate cases is at the discretion of the district court, but often courts balance considerations of efficiency, expense and fairness. *See United States v. Dentsply Int'l, Inc.*, 190 F.R.D. 140, 142-43 (D Del 1999). Because the '488 patent involves the expression of *Bt* genes in corn, an interpretation of the patent and any infringement necessarily involves some of the same questions at issue in the BTC I action [FN1]. At issue in this motion is whether, at this stage in the BTC I litigation, it is too late to consolidate the cases without adding undue delay to an already ripe BTC I case.

FN1 Plaintiff cites the following commonalities: (1) parties; (2) products at issue; (3) underlying technology; (4) documents/exhibits; (5) legal claim (patent infringement); (6) defendants will likely assert the same defenses; (7) the patent at issue in BTC II shares similarities with the patents at issue in BTC I; and (8) the same people will be witnesses in both actions (D I 206 at 4-5).

*2 Plaintiff argues that consolidating the cases will not prejudice the defendants because the November 29, 2004, trial date can be adjusted, and that consolidation is more efficient because the parties will not have to litigate the same issues twice. Defendants contest consolidation on four grounds: (1) consolidation will complicate the proceedings; (2) will lead to delay and increased costs because the new patent will require discovery on the same level as the discovery that took place in BTC I (notably the discovery went on for more than a year and a half); (3) the consolidation prejudices them because, if plaintiff had disclosed the '488 patent when the notice of allowance was issued, the defendants could have included it in their subsequent discovery; and (4) the efficiency realized through consolidation can be achieved through other means, namely staying the BTC II action and application of claim preclusion.

The BTC I case is scheduled to go to trial this November. At this point in time, and in light of the courts already tight schedule, the trial date could not be rescheduled without undue delay. In

addition, the BTC I case alone is highly complex. Adding another patent to the plaintiff's claims will only increase the case's complexity and make it that much harder for a jury to come to a resolution. For all of these reasons, the court concludes that consolidation of the two cases would be more burdensome than beneficial.

IV CONCLUSION

Therefore, at Wilmington this 27th day of August, 2004;

IT IS ORDERED that plaintiff's motion to consolidate (D I 205) is denied.

2004 WL 2002208 (D Del.)

Motions, Pleadings and Filings (Back to top)

1:02CV01331 (Docket)

(Jul. 25, 2002)

END OF DOCUMENT

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on March 15, 2005, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

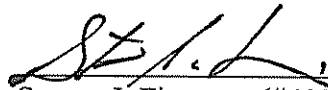
VIA HAND DELIVERY

Josy W Ingersoll, Esquire
Young Conaway Stargatt & Taylor, LLP
The Brandywine Building
1000 West Street, 17th Floor
P O Box 391
Wilmington, DE 19899-0391

I hereby certify that on March 15, 2005, I have sent by Federal Express, the foregoing document to the following non-registered participants.

BY FEDERAL EXPRESS

James Galbraith
Maria Luisa Palmese
Anthony Pfeffer
Kenyon & Kenyon
One Broadway
New York, NY 10004


Steven J. Fineman (#4025)
Richards, Layton & Finger, P.A.
One Rodney Square
P.O. Box 551
Wilmington, Delaware 19899
(302) 651-7700
Fineman@rlf.com